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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

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39

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	08/823999	ROGERS
	Examiner	Art Unit
	GAMBEL	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/23/03 BY BD APPEALS

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1-12

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 7, 9

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1-6, 8, 10-12

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

PAPER NO. 39

DETAILED ACTION

1. The Vacatur of Rejections and Remand to the Examiner (Paper No. 38), mailed 4/23/03, by the Board of Patent Appeals and Interferences is acknowledged.

2. Claims 1-12 are pending.

Claims 1-6, 8 and 10-12 are being acted upon as they read on methods of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof comprising administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte-integrin mediated adhesion or function wherein the compound is an antibody or antibody fragment that is immunoreactive with Mac-1 (CD11b/CD18).

Claims 7 and 9 have been withdrawn from consideration as they read on the non-elected limitations.

Claim 7 has been withdrawn from consideration as it reads on methods of inhibiting or reducing stenosis or restenosis with a compound which is an antibody or an antibody fragment that is immunoreactive with a ligand selected from the group consisting of ICAM-1, fibrinogen, C3bi and factor X.

If claim 7 is intended to encompass the elected invention of methods employing anti-Mac-1 antibodies wherein the anti-Mac-1 antibodies inhibits Mac-1 directly and inhibits the interaction of Mac-1 with a ligand selected from the group consisting of ICAM-1, fibrinogen, C3bi and factor X, then claim 7 would read on the elected invention.

Applicant should indicate the intent of claim 7 and address the rejection under 35 USC 112, second paragraph, set forth herein concerning the antecedent basis of claim 7.

Claims 13-17 have been canceled previously.

3. The Board of Appeals has made the following of record (see Paper No. 38).

A) Taber's Cyclopedic Medical Dictionary, 18th Ed., pp. 130, 1666 and 1828 (1997) (892; of record) sets forth the following definitions.

Stenosis: The constriction or narrowing of a passage or orifice.
Aortic Stenosis: Narrowing of the aorta or its orifice due to lesion of the wall with scar formation.
Restenosis: The recurrence of a stenotic condition as in a hear valve or vessel.

In response to the Board's request (page 3 of Paper No. 38), applicant is invited to distinguish "stenosis", "restenosis" and "dependent restenosis".

In distinguishing these "limitations", applicant should address these "limitations" in the context of the circumstances of the claimed methods. For example, the instant methods encompass patients undergoing angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery or transplantation of cell, tissue or organs (e.g., see claim 3).

For example, applicant is invited to indicate whether there is a manipulative difference between administering an effective inhibitory amount of an antibody that binds -Mac-1 (e.g. 0.25 mg/kg - 1.0 mg/kg) in a patient undergoing one of the procedures set forth in claim 3 and the instant claims.

In addition, rejections under 35 USC 112, first and second paragraph, has been included herein as there is an ambiguity concerning the claimed limitations and what constitutes prior art against said limitations.

B) The Board has invited the application of Genetta et al. (ABCIXMAB: A New Antiaggregant Used in Angioplasty, Annals of Pharmacotherapy 30: 251-257 (March 1996) as the closest prior art.

It is noted that abciximab taught by Genetta et al. (Ann Pharmacol. 30: 251-257, 1996) is the same c7E3 antibody taught by Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) (1449) and Coller et al. (U.S. Patent No. 5,976,532), both of record.

c7E3, abciximab and ReoPro are all drawn to essentially the same inhibitory anti-GPIIb/IIIa 7E3 antibody which crossreacts with both $\alpha_v\beta_3$ and Mac-1.

4. The following excerpt from Fattori et al. (Lancet 361: 247-249, 2003; see page 247-248, Mechanisms of Restenosis and Preventing Restenosis) is set forth in the interest of setting some groundwork to the issues set forth in the instant application.

"Mechanisms of Restenosis:

Restenosis is the reduction of the luminal size due to loss of gain in lumen size after intravascular interventional procedures. Several cellular and molecular events occur sequentially after a vascular injury. The initial response of the elastic fibers of the vascular wall to overstretching by balloon catheter is elastic recoil, response for the loss of gain, which characterises the early phase or restenosis. The endothelial denudation and the exposure of the subintimal components cause platelet adherence and aggregation, fibrinogen binding, and thrombus formation. Thrombus formation can also act as a scaffold into which vascular smooth muscle cells can migrate, synthesise matrix and collagen, and reorganise the thrombus, providing the substrate for neointimal formation. Activated platelets release several mitogens and chemotactic factors, which stimulate smooth muscle cell migration and proliferation into the injury site. Inflammatory mediators and cellular elements contribute to trigger a complex array of events that modulate matrix production and cellular proliferation. Finally, remodeling, a gradual dynamic process mediated by adventitial myofibroblasts that leads to a change in vessel size by constrictive remodeling without an overall change in tissue volume, contributes to the loss of lumen at later time. Stenting reduces elastic recoil and negative remodeling, the mechanical components of restenosis, but also stimulates the cellular mechanisms yielding to in-stent restenosis.

By contrast with balloon angioplasty, restenosis after stenting is due mostly to neointimal formation. The bulk of in-stent restenosis consists of extracellular matrix, proteoglycans, and collagen, with only 11% cells. Greater neointimal proliferation is associated with deeper medial penetration of stent struts, contradicting the idea that in percutaneous coronary intervention a larger lumen achieved by angioplasty diminishes the rate of restenosis. Moreover arterial medial disruption and lipid-core penetration by stent struts is associated with greater numbers of inflammatory cells by contrast with strut in contact with fibrous plaque, highlighting the role of inflammation in restenosis and its relation with the morphology of the atherosclerotic plaque.

Preventing Restenosis

Much research into many mechanical devices and drugs has been done to prevent restenosis, providing the rationale for an enormous number of clinical trials, but none have been proven to be effective. Many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process. Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, cholesterol-lowering agents, and antioxidants has proven almost universally negative. These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to insufficient concentration of drug at the injury site or lack of chronic dosing. In general, although animal models provide new insight into the mechanism of restenosis, biological and mechanical differences meant that therapeutic success of anti-restenoic therapies was not achieved in human beings."

5. Applicant is invited to clarify the claimed limitations, particularly as they read on the claimed therapeutic endpoints. In particular, applicant is invited to clarify what constitutes the claimed limitations in the context of the patient (e.g., animal model or human), inhibiting or reducing stenosis or restenosis (e.g. parameters and under what conditions) and "amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" (e.g. dosage of anti-Mac-1 antibody).

It is acknowledged that the claims are read in light of the elected invention as it reads on methods of inhibiting restenosis or stenosis with anti-Mac-1 antibodies.

In the interest of compact prosecution, the following rejections under 35 U.S.C. § 112, first paragraph, written description and enablement, are drawn to the recitation and scope of "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18) and CD11d/CD18 in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue", currently recited in the instant claims.

In addition, enablement issues are raised with respect to the ability of anti-Mac-1 antibodies to reduce or inhibit stenosis or restenosis in humans undergoing cardiovascular procedures.

Applicant should provide independent claims drawn to the elected invention.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, including the specificity of claimed/elected compounds.

7. Applicant is invited to review to the length of the Abstract to determine if it exceeds 150 words in length. See MPEP 608.01(b).

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 1-6, (7), 8, (9) and 11-12 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" currently recited in the instant claims because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the claimed "compounds" including "antibodies, molecules, peptides and peptiodmimetics", as currently claimed, or "ligands, proteins, antisense oligonucleotides and riibozymes", as currently disclosed, encompass patentably distinct adhesion molecules (and pathways) and inhibitory compounds, wherein the compounds as well as the adhesion molecules differ in structure and modes of action (see Composition on pages 9-20 of the instant specification). The "compounds" encompass distinct and diverse structures and do not encompass common structural elements essential to the common utility of "specifically inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue".

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species of "compounds which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function" such as the exemplified anti-Mac-1 antibodies in an experimental animal model to support an entire genus of diverse and unrelated molecules and adhesion pathways. The instant invention encompasses any "compound" or antagonist that results in the desired binding and inhibitory effect on an the integrin or ligand selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18) and CD11d/CD18, yet the instant specification does not provide sufficient written description as to the structural features of said "compounds" and the correlation between the chemical structure and the desired binding and inhibitory function.

The reliance on the disclosed limited number of known adhesion molecules or adhesion molecule-specific antibodies does not support the written description of any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function", including any "antibody", molecule, peptide or peptidomimetic". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed "compounds" other than certain adhesion molecules or adhesion molecule-specific antibodies would be expected to have greater differences in their activities. "Compounds" encompassing "antibodies, ligands, proteins, antisense oligonucleotides, ribozymes and peptidomimetics" rely upon a myriad of distinct and diverse structures and do not encompass common structural elements essential to the common utility of "specifically inhibiting or reducing leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue".

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Hemker et al. (Emerging Drugs 4: 175-195, 1999) disclose that the hemostatic-thrombotic system is a non-linear system containing a number of nested positive and negative feedback loops and that at the present state of knowledge it is impossible to predict the effect of inhibition of a single reaction on the response of the complete system. For this reason, one cannot predict the antithrombotic potency of a compound from its biochemical properties. See entire document, including Summary on page 175.

In addressing the issue of restenosis with emerging therapies in cardiology and haemotology, Pimanda et al. (Curr. Drug Targets Cardiovas. Haematol. Disord 3 (2): 101-123, 2003) discloses that from the 1980's to the present numerous drugs tested in animal models - particularly the pig - have suggested benefit, although until recently none have shown benefit in humans (see entire document, including Strategies to Reduce Restenosis on pages 101-102, overlapping paragraph). These authors conclude that "as the extent of the biological complexity of cell growth and regulation is understood, the unbrideled enthusiasm at the dawn of the molecular era now has been tempered by a sense of reality. From the current evidence, it is likely that many drugs under development that target a particular molecular defect may prove ineffective alone and will probably need to be used in combination with cytotoxics in current use to achieve disease remission. (see the first paragraph of the Conclusion on page 117).

Fattori et al. (Lancet 361: 247-249, 2003) notes that "many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process" (see Preventing Restenosis on page 247). "Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin converting-enzyme inhibitors, cholesterol-lowering agents and antioxidants has proven almost universally negative."

Welt et al. (Arterioscler Thromb Vasc Biol 22: 1769-1776, 2002) notes that "studies of restenosis are limited by the fact that direct tissue examination is only rarely possible" (see page 1769, column 2, paragraph). Here, the authors further acknowledge that "animal models are not perfect mirrors of human pathology, and as proof, there are numerous examples of therapies that are effective in animals but not in humans. Therefore, animal studies are best used to answer specific biological questions that give insight into human disease rather than to provide exact surrogates of human pathology." Also, see entire document, including Implications for Antirestenotic Therapies on pages 1772-1774.

Topol et al. (JAMA 278: 479-484,1997) notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the β3 integrin (see Introduction on page 479).

Applicant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: "No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant specification).

Others have relied upon the same or similar models as applicant's single experimental model with similar positive results only to observe the lack of positive results or efficacy in human clinical trials.

It is noted that page 23, paragraph 2 of the instant specification discloses: "For reference, applicant's reliance upon the profound inhibition of experimental restenosis by M1/70, equal to or greater than the inhibition achieved in this same animal model by "gold-standard" experimental antiproliferative agents such as heparin and others, discussed by Rogers et al. (Circulation 88: 1215-1221, 1995)."

Heparin can inhibit smooth muscle proliferation and does bind Mac-1 (Diamond et al., J. Cell Biol. 130 : 1473 - 1482, 1995). Despite its well known use as an anticoagulant, heparin has failed to show beneficial effects on restenosis (Dangas et al., Am Heart J. 132: 428-436, 1996, particularly page 431, column 1).

Further, it is noted that anti-CD18 antibodies have different effects on leukocyte extravasation, smooth muscle migration, intimal thickening and infarct size depending on the system under observation.

For example, Kling (Arteriosclerosis and Thrombosis 12: 997-1007, 1992) disclose that smooth muscle cells moved into the intima despite complete blockage of neutrophils with the potent inhibitor of leukocyte adhesive functions anti-CD18 antibody in an experimental model (see entire document, including the Abstract).

Kling et al. (Circulation Research 77: 112-~~1~~128, 1995) discloses that an anti-CD18 antibody in combination with anti-VLA-4 antibody can block mononuclear leukocyte emigration, thereby reducing smooth muscle cell migration in an experimental animal model (see entire document, including the Abstract and Discussion).

However, Faxon et al. (J Am Coll Cardiol 40: 1199-~~20~~1204, 2002) disclose that while experimental studies have demonstrated that the inhibition of CD11/CD18 has resulted in significant reduction of infarct size and improved endothelial function, coronary blood flow, and left ventricular hemodynamics (See Introduction), an antibody to CD11/CD18 did not reduce infarct size in patients who underwent primary angioplasty (see entire document, including the Abstract and Discussion). Similar results were observed in patients with acute myocardial infarction receiving thrombolysis (see page 1203, column 1, lines 2-8).

For example, the instant specification relies upon screening for peptide and peptidomimetics compounds (pages 11-13) as well as screening for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds (pages 13-19). The specification appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by Altieri et al. J. Biol. Chem. 268: 1847-1853 (1993) (see page 12, paragraph 3 of the specification). As indicated above, the only observation provided by the specification as filed is the administration of the anti-Mac-1 antibody M1/70 in an experimental animal model.

With respect to the breadth of "compounds", there is insufficient written description of the wide variety of distinct and diverse compounds (e.g. molecules, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds) which do not share a common structure that contributes to a common ability either to inhibit integrin-mediated interactions or to inhibit stenosis / restenosis.

For example, applicant relies upon theoretical calculations and empirical findings for providing guidance for the design of oligonucleotides to inhibit gene expression and yet no written description of such inhibitory oligonucleotides compounds are disclosed in the specification as filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

There is insufficient written description of the claimed compounds broadly encompassed by the claimed invention. There is a lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse compounds employed in the claimed methods. While the specification discloses a starting point for screening or testing for compounds that inhibit or reduce leukocyte integrin-ligand interactions, the instant disclosure does not set forth any procedures that will necessarily lead to discovery for such a compound and it does not identify suitable members of compounds such as peptidomimetics, antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds.

The application does not more than describe the desired function of the claimed compounds broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon finding "a compound that specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue". Without such a compound, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the compound(s) that is (are) essential to practice the method. Without possession of the compound(s), the claimed endpoints are illusory and there is no meaningful possession of the method.

Applicant has not provided sufficient written description of a "compound which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" broadly encompassed by the claimed invention.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

Therefore, the elected invention of anti-Mac-1 antibodies (and given evidence, certain soluble adhesion molecules and adhesion molecule-specific antibodies as well as the fibrinogen peptide discussed above disclosed in the specification as filed), but not the full breadth of the claimed "compounds", meet the written description provision of 35 USC 112, first paragraph.

10. Claims 1-6, (7), 8, (9), 10 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as pharmacological compounds which inhibit stenosis or restenosis can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo evidence of inhibiting leukocyte-integrin-mediated adhesion with Mac-1-specific antibodies in an experimental model accurately reflects the relative efficacy of the claimed methods relying upon any "compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion or function" (e.g. compounds, molecules, peptides, peptidomimetics, anti-sense oligonucleotides, etc.) or that anti-Mac-1 antibodies can inhibit or reduce stenosis or restenosis in humans (e.g. undergoing cardiovascular procedures as set forth in instant claim 3).

Although the claims are read in the context of the anti-Mac-1 antibodies as the elected compound of the claimed invention; the following is noted as the claims read on "a compound which specifically inhibits or reduces leukocyte-integrin-mediated adhesion".

The claimed "compounds" encompass any compound, integrin, ligand, molecule, peptide or peptidomimetic or others disclosed on pages 9-20 of the instant specification, which are disclosed and asserted to be capable of inhibiting or reducing leukocyte-integrin-mediated adhesion to inhibit or reduce stenosis or restenosis. However, the claims do not recite sufficient structural elements or specificity for the "compounds" encompassed by the claimed methods. The specification does not provide sufficient guidance and direction to identify and to enable any "compound" which might inhibit or reduce leukocyte-integrin-mediated adhesion which inhibits or reduces stenosis or restenosis, including achieving these therapeutic endpoints in humans.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4) (1449).

The success of state of the art structure-based strategies for inhibitor design is highly unpredictable. For example, Kuntz, Science (1992) 257:1078-1031 on page 1080, column 3, discloses that as little as 2% of compounds predicted to inhibit specific enzymatic or receptor systems actually show inhibition in the micromolar range. Kuntz further discloses that "optimization" of these compounds has proven even more problematic.

Hemker et al. (Emerging Drugs 4: 175-195, 1999) disclose that the hemostatic-thrombotic system is a non-linear system containing a number of nested positive and negative feedback loops and that at the present state of knowledge it is impossible to predict the effect of inhibition of a single reaction on the response of the complete system. For this reason, one cannot predict the antithrombotic potency of a compound from its biochemical properties. See entire document, including Summary on page 175.

In addressing the issue of restenosis with emerging therapies in cardiology and haemotology, Pimanda et al. (Curr. Drug Targets Cardiovas. Haematol. Disord 3 (2): 101-123, 2003) disclose that "from the 1980's to the present numerous drugs tested in animal models - particularly the pig - have suggested benefit, although until recently none have shown benefit in humans" (see entire document, including Strategies to Reduce Restenosis on pages 101-102, overlapping paragraph). These authors conclude that "as the extent of the biological complexity of cell growth and regulation is understood, the unbrideled enthusiasm at the dawn of the molecular era now has been tempered by a sense of reality. From the current evidence, it is likely that many drugs under development that target a particular molecular defect may prove ineffective alone and will probably need to be used in combination with cytotoxics in current use to achieve disease remission". (see the first paragraph of the Conclusion on page 117).

Fattori et al. (Lancet 361: 247-249, 2003) notes that "many different biological mechanisms contribute to restenosis and drugs that target only one pathway for a restricted period may have limited value in a multifactorial process" (see Preventing Restenosis on page 247). "Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin converting-enzyme inhibitors, cholesterol-lowering agents and antioxidants has proven almost universally negative."

Welt et al. (Arterioscler Thromb Vasc Biol 22: 1769-1776, 2002) notes that "studies of restenosis are limited by the fact that direct tissue examination is only rarely possible" (see page 1769, column 2, paragraph). Here, the authors further acknowledge that "animal models are not perfect mirrors of human pathology, and as proof, there are numerous examples of therapies that are effective in animals but not in humans. Therefore, animal studies are best used to answer specific biological questions that give insight into human disease rather than to provide exact surrogates of human pathology." Also, see entire document, including Implications for Antirestenotic Therapies on pages 1772-1774.

Topol et al. JAMA 278: 479-484,1997, which notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the β3 integrin (see Introduction on page 479).

Applicant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: "No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant specification).

Others have relied upon the same or similar models as applicant's single experimental model with similar positive results only to observe the lack of positive results or efficacy in human clinical trials.

It is noted that page 23, paragraph 2 of the instant specification discloses: "For reference, applicant's reliance upon the profound inhibition of experimental restenosis by M1/70, equal to or greater than the inhibition achieved in this same animal model by "gold-standard" experimental antiproliferative agents such as heparin and others, discussed by Rogers et al. (Circulation 88: 1215-1221, 1995)."

Heparin can inhibit smooth muscle proliferation and does bind Mac-1 (Diamond et al., J. Cell Biol. 130 : 1473 - 1482, 1995). Despite its well known use as an anticoagulant, heparin has failed to show beneficial effects on restenosis (Dangas et al., Am Heart J. 132: 428-436, 1996, particularly page 431, column 1).

Further, it is noted that anti-CD18 antibodies have different effects on leukocyte extravasation, smooth muscle migration, intimal thickening and infarct size depending on the system under observation.

For example, Kling et al. (Arteriosclerosis and Thrombosis 12: 997-1007, 1992) disclose that smooth muscle cells moved into the intima despite complete blockage of neutrophils with the potent inhibitor of leukocyte adhesive functions anti-CD18 antibody in an experimental model (see entire document, including the Abstract).

Kling et al. (Circulation Research 77: 112- 128, 1995) disclose that an anti-CD18 antibody in combination with anti-VLA-4 antibody can block mononuclear leukocyte emigration, thereby reducing smooth muscle cell migration in an experimental animal model (see entire document, including the Abstract and Discussion).

However, Faxon et al. (J Am Coll Cardiol 40: 1199-1204, 2002) disclose that while experimental studies have demonstrated that the inhibition of CD11/CD18 has resulted in significant reduction of infarct size and improved endothelial function, coronary blood flow, and left ventricular hemodynamics (See Introduction), an antibody to CD11/CD18 did not reduce infarct size in patients who underwent primary angioplasty (see entire document, including the Abstract and Discussion). Similar results were observed in patients with acute myocardial infarction receiving thrombolysis (see page 1203, column 1, lines 2-8).

The instant specification relies upon screening for peptide and peptidomimetics compounds (pages 11-13) as well as screening for antisense oligonucleotides, nucleic acid regulators, molecules from a complex mixture of random molecules, natural products and synthetic chemical compounds (pages 13-19). The specification appears to disclose only one peptide, that is, a particular fibrinogen fragment which modifies fibrinogen to Mac-1 described by Altieri et al. J. Biol. Chem. 268: 1847-1853 (1993) (see page 12, paragraph 3 of the specification). As indicated above, the only observation provided by the specification as filed is the administration of the anti-Mac-1 antibody M1/70 in an experimental animal model.

The claims are not limited to the use of a single class of compounds but rather encompass a broad range of distinct compounds and specificities. The claimed methods encompass targeting a variety of integrin members (e.g. CD11a/CD18; CD11b/CD18; CD11c/CD18; CD11d/CD18) (or their ligands) and administering a variety of structural diverse compounds (e.g. antibodies, molecules, peptides, peptidomimetics, antisense oligonucleotides, ribozymes).

There is insufficient objective evidence that a single compound such as the M1/70 antibody in experimental models, as disclosed in the specification as filed, can be extrapolated to predict the efficacy of a myriad of diverse "compounds that inhibit or reduce leukocyte mediated adhesion or function" (e.g. molecules, peptides, peptidomimetics, oligonucleotides) in the claimed methods to inhibit or reduce stenosis or restenosis, commensurate in scope with the claimed invention.

Further, it appears that compounds that can bind Mac-1 such as heparin and anti-CD18 antibodies do not result in the inhibition of stenosis or restenosis in humans, despite success in various experimental model systems, including experimental model systems that mimic that relied upon for the anti-Mac-1 M1/70 antibody in the instant specification.

There is insufficient objective evidence that the skilled artisan would predict that such a diverse class of compounds specific for various targets would be recognized as a single class of compounds to reduce or inhibit stenosis or restenosis of a blood vessel following injury to vascular tissue.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species such as anti-Mac-1 antibodies in an experimental model to support an entire genus of diverse and structurally unrelated compounds targeting a diverse adhesion molecules ligand-receptor molecules, interactions and functions. The instant invention encompasses any "compound which specifically reduces or inhibits leukocyte integrin-mediated adhesion or function" that results in the desired reduction or inhibition of stenosis or restenosis", yet the instant specification does not provide sufficient guidance and direction as to the structural features of said "compounds" and the correlation between the chemical structure and the desired binding and inhibitory function. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated binding antagonists encompassed by the claimed binding "compounds" would be expected to have greater differences in their activities

The specification describes assays for determining whether a given compound possess certain desired characteristics and identifies some broad categories of compounds that might work, these description without more precise guidelines amount to little more that a starting point, a direction for further research . The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

The scope of the required enablement varies inversely with the degree of predictability involved and in cases involving unpredictable factors such as physiological activity more may be required. See MPEP 2164.03 and 2164.02.

Given the relatively incomplete understanding in the biotechnological field involved and the lack of a reasonable correlation between the narrow disclosure in the specification and broad scope of protection sought in the claims; the lack of enablement is deemed appropriate. See MPEP 2164.08.

In view of the lack of predictability of the art to which the invention pertains, methods of reducing or inhibiting stenosis or restenosis with a broad range of structurally diverse "compounds" to a variety of diverse specificities would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies for inhibiting restenosis and stenosis, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive for the breadth of "compounds" which specifically inhibits or reduces leukocyte-integrin-mediated adhesion that reduce or inhibit stenosis and restenosis.

Given the ambiguity or issues associated with the claimed limitations as well as the evidence set forth herein, particulary as they read on inhibiting stenosis and restenosis in humans, the claimed methods as they read on inhibiting stenosis and restenosis with anti-Mac-1 antibodies are also subject to this rejection under 35 USC 112, first paragraph, enablement.

11. Claims 1-6, (7), 8, (9) and 10-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

A) Claims 1-6, (7), 8, (9) and 10-12 are indefinite in the recitation of " a method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of a patient in need of treatment thereof comprising administering ... a compound which specifically inhibit or reduce leukocyte integrin-mediated adhesion or function wherein the integrin is selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18) and CD11d/CD18, wherein ... in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" because the parameters by which the metes and bounds are the claimed endpoints are ill-defined and ambiguous.

There is ambiguity as to the standard for ascertaining the requisite degree and nature of the particular parameters by which the ordinary artisan determines achieving the claimed method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue ... wherein (the compound is administered) ... in an amount effective to inhibit or reduce stenosis or dependent function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

As indicated above, the Board of Appeals has made the following of record (see Paper No. 38).

Taber's Cyclopedic Medical Dictionary, 18th Ed., pp. 130, 1666 and 1828 (1997) (892; of record) sets forth the following definitions.

Stenosis: The constriction or narrowing of a passage or orifice.
Aortic Stenosis: Narrowing of the aorta or its orifice due to lesion of the wall with scar formation.
Restenosis: The recurrence of a stenotic condition as in a hear valve or vessel.

In response to the Board's request (page 3 of Paper No. 38), applicant is invited to distinguish "stenosis", "restenosis" and "dependent restenosis".

In distinguishing these "limitations", applicant should address these "limitations" in the context of the circumstances of the claimed methods.

For example, the instant methods encompass patients undergoing angioplasty, atherectomy, endovascular stenting, coronary artery by pass surgery, peripheral bypass surgery or transplantation of cell, tissue or organs (e.g., see claim 3).

For example, applicant should address which parameters are encompassed by the claimed limitaitons and whether achieving such parameters are limited to either experimental or human clinical observations.

Applicant is invited to indicate whether there is a manipulative difference between administering an effective inhibitory amount of an antibody that binds -Mac-1 (e.g. 0.25 mg/ kg - 1 mg/kg) in a patient undergoing one of the procedures set forth in instant claim 3.

With respect to the metes and bounds of restenosis, the following is noted.

Anderson (Disease-a-Month 39(9): 617-670 (1993) discloses that twelve different definitions of restenosis have been counted and the existence of so many definitions has led to confusion (page 642-648, particularly page 642, paragraph 1, Defining Clinical Restenosis). Restenosis by one set of criteria is not necessarily equivalent to restenosis by another set of criteria.

As set forth above, the following excerpt from Fattori et al. (Lancet 361: 247-249, 2003; see page 247-248, Mechanisms of Restenosis and Preventing Restenosis) indicates that the mechanisms of restenosis differs between balloon and in-stent catheters set forth in the interest of setting some groundwork to the issues set forth in the instant application.

"Mechanisms of Restenosis:

Restenosis is the reduction of the luminal size due to loss of gain in lumen size after intravascular interventional procedures. Several cellular and molecular events occur sequentially after a vascular injury. The initial response of the elastic fibers of the vascular wall to overstretching by balloon catheter is elastic recoil, response for the loss of gain, which characterises the early phase or restenosis. The endothelial denudation and the exposure of the subintimal components cause platelet adherence and aggregation, fibrinogen binding, and thrombus formation. Thrombus formation can also act as a scaffold into which vascular smooth muscle cells can migrate, synthesise matrix and collagen, and reorganise the thrombus, providing the substrate for neointimal formation. Activated platelets release several mitogens and chemotactic factors, which stimulate smooth muscle cell migration and proliferation into the injury site. Inflammatory mediators and cellular elements contribute to trigger a complex array of events that modulate matrix production and cellular proliferation. Finally, remodeling, a gradual dynamic process mediated by adventitial myofibroblasts that leads to a change in vessel size by constrictive remodeling without an overall change in tissue volume, contributes to the loss of lumen at later time. Stenting reduces elastic recoil and negative remodeling, the mechanical components of restenosis, but also stimulates the cellular mechanisms yielding to in-stent restenosis.

By contrast with balloon angioplasty, restenosis after stenting is due mostly to neointimal formation. The bulk of in-stent restenosis consists of extracellular matrix, proteoglycans, and collagen, with only 11% cells. Greater neointimal proliferation is associated with deeper medial penetration of stent struts, contradicting the idea that in percutaneous coronary intervention a larger lumen achieved by angioplasty diminishes the rate of restenosis. Moreover arterial medial disruption and lipid-core penetration by stent struts is associated with greater numbers of inflammatory cells by contrast with strut in contact with fibrous plaque, highlighting the role of inflammation in restenosis and its relation with the morphology of the atherosclerotic plaque."

The instant specification does not distinctly define the metes and bounds of "stenosis" or "restenosis" or more particularly, the endpoints of "inhibiting or reducing stenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof ... in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue", as currently claimed.

Page 21, paragraph 1 of the instant specification discloses that: "Those of skill in the art can readily determine an effective concentration for treating a patient in need thereof typically based on extrapolation form animal data and from correlations established during clinical trials. Dosages will be dependent on the type of compound and route of administration. For example, in the case of monoclonal antibody suitable concentrations range from between 0.25 mg/Kg to 1 mg/Kg."

The instant methods encompass the inhibition of integrin-mediated (e.g. Mac-1-mediated) leukocyte adhesion and/or function, especially the adhesion and function of monocytes and granulocytes resulting in the inhibition of neointimal hyperplasia (e.g. see pages 6-7 of the instant specification; Detailed Description of the Invention).

Alternatively, it would appear that the instant methods encompass treating patients undergoing angioplasty, atherectomy, endovascular stenting, coronary artery by pass surgery, peripheral bypass surgery or transplantation of cell, tissue or organs (e.g., see claim 3) with anti-Mac-1 in a concentration range from between 0.25 mg/Kg to 1 mg/Kg.

Applicant has relied upon animal models of arterial injury and neointimal hyperplasia that study the cellular events which lead to restenosis in humans, to devise strategies to suppress tissue growth in an attempt to reduce restenosis and enhance long term clinical results (e.g. see page 2, paragraph 1 of the instant specification).

Yet applicant acknowledges that no pharmacological agent has yet been shown to reduce restenosis in humans (e.g. see page 2, paragraph 2 of the instant specification).

Welt et al. (Arterioscler Thromb Vasc Biol 22: 1769-1776, 2002) notes that "studies of restenosis are limited by the fact that direct tissue examination is only rarely possible" (see page 1769, column 2, paragraph). Here, the authors further acknowledge that "animal models are not perfect mirrors of human pathology, and as proof, there are numerous examples of therapies that are effective in animals but not in humans. Therefore, animal studies are best used to answer specific biological questions that give insight into human disease rather than to provide exact surrogates of human pathology." Also, see entire document, including Implications for Antirestenotic Therapies on pages 1772-1774.

It is noted that the co-inventors have acknowledged in publications that the 7E3 antibody inhibits restenosis, as reported in Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) (1449) and Simon et al. (Thromb. Vasc. Biol. 17: 528-535, 1997).

This is consistent with applicant's submission of Topol et al. (JAMA 278: 479-484,1997), which notes that a large number of pharmacological agents have failed to reduce restenosis or improve long-term outcomes and the only large-scale trial that reported an effect was the 23% reduction in clinical recurrence at 6 months using abciximab, a monoclonal fragment directed against the β3 integrin (see Introduction on page 479).

Similarly, Genetta et al. (Ann Pharmacol. 30: 251-257, 1996) teach the results of clinical trials which have indicated that abciximab can reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients, plays a role in the treatment of unstable angina and acute therapy of myocardial infarctions (see entire document, including Data Synthesis on page 251, column 1 and Clinical Trials on pages 253-254).

Bendeck et al. (J. Vasc. Res. 38: 590-599, 2001) and Wu et al. (Thrombosis Research 101: 127-138, 2001) both disclose the ability of the 7E3 antibody / Abciximab antibody to inhibition smooth muscle cell migration resulting in a decrease in neointimal hyperplasia and lumen occlusion (See entire documents, including the Abstracts).I

However, applicant also has relied upon post-filing date observations to indicate that the 7E3 antibody does not inhibit restenosis in certain in-stent patient populations (e.g. The ERASER Investigators, Circulation 100: 799-806, 1999).

One of ordinary skill in the art clearly has recognized that there are differences between experimental and clinical conditions as well as differences between the endpoints one relies upon in the various conditions and when one measures the particular parameter(s) (e..g. balloon versus in-stent).

On one hand, applicant asserts enablement of a broad range of claimed compounds, including the single exemplification of anti-Mac-1 antibody in an experimental model to support the limitations of the claimed methods.

However, applicant also acknowledges the differences between the attempts to go from the experimental models to the achieving clinical success in stating: "No pharmacologic agent has yet been shown to reduce restenosis in humans" (see page 2, paragraph 2 of the instant specification).

Others have relied upon the same or similar models as applicant's single experimental model with similar positive results only to observe the lack of positive results or efficacy in human clinical trials.

It is noted that page 23, paragraph 2 of the instant specification discloses: "For reference, applicant's reliance upon the profound inhibition of experimental restenosis by M1/70, equal to or greater than the inhibition achieved in this same animal model by "gold-standard" experimental antiproliferative agents such as heparin and others, discussed by Rogers et al. (Circulation 88: 1215-1221, 1995)."

Although heparin can inhibit smooth muscle proliferation and does bind Mac-1 (Diamond et al., J. Cell Biol. 130 : 1473 - 1482, 1995) and its well known use as an anticoagulant, heparin has failed to show beneficial effects on restenosis (Dangas et al., Am Heart J. 132: 428-436, 1996, particularly page 431, column 1).

Further, it is noted that anti-CD18 antibodies have different effects on leukocyte extravasation, smooth muscle migration, intimal thickening and infarct size depending on the system under observation.

For example, Kling (Arteriosclerosis and Thrombosis 12: 997-1007, 1992) disclose that smooth muscle cells moved into the intima despite complete blockage of neutrophils with the potent inhibitor of leukocyte adhesive functions anti-CD18 antibody in an experimental model (see entire document, including the Abstract).

Kling et al. (Circulation Research 77: 112-~~7~~128, 1995) discloses that an anti-CD18 antibody in combination with anti-VLA-4 antibody can block mononuclear leukocyte emigration, thereby reducing smooth muscle cell migration in an experimental animal model (see entire document, including the Abstract and Discussion).

However, Faxon et al. (J Am Coll Cardiol 40: 1199-~~204~~1204, 2002) disclose that while experimental studies have demonstrated that the inhibition of CD11/CD18 has resuled in significant reduction of infarct size and improved endothelial function, coronary blood flow, and left ventricular hemodynamics (See Introduction), an antibody to CD11/CD18 did not reduce infarct size in patients who underwent primary angioplasty (see entire document, including the Abstract and Discussion). Similar results were observed in patients with acute myocardial infarction receiving thrombolysis (see page 1203, column 1, lines 2-8).

There is an ambiguity concerning which parameters or endpoints are encompassed by the claimed methods of "inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof ... in an following injury to vascular tissue", as currently claimed amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel

There is an ambiguity with respect to the claimed endpoints in that it is unclear whether "the administration of an antibody that binds Mac-1 in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue" is an anti-Mac-1 antibody that inhibits leukocyte adhesion / function, smooth muscle migration or intimal hyperplasia in an in vitro experimental model, in an in vivo experimental model, in balloon angioplasty or in in-stent angioplasty and, in turn, what is the effective amount of said antibody.

The claims do not recite specific measurable endpoints per se but rather recite broad methods of "inhibiting or reducing stenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof ... in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue".

Clearly, the claims encompass various endpoints and properties that can vary upon the particular experimental or clinical setting as well as the particular timepoint observed.

This is further complicated by applicant's position that prior art pharmacological agents which have been able to inhibit restenosis or intimal hyperplasia in experimental models are not enabled in humans, yet applicant's reliance upon the application of one particular anti-Mac-1 antibody in a similar experimental model is enabled for that antibody as well as for a broad genus of compounds.

B) Claims 5 and 6 (and nonelected claims 7 and 9) are indefinite with respect to the antecedent basis of "integrin" and "ligand" because it is ambiguous as to whether the "integrin" or "ligand" is the specificity of the claimed compound / antibody or whether the "integrin" or "ligand" is the specificity of the claim interaction, that is, whether the "integrin" or "ligand" is the counterreceptor of the targeted specificity. For example, an anti-Mac-1 antibody can block Mac-1-mediated interactions, either by binding to Mac-1 itself or by binding to a Mac-1 ligand selected from the group consisting of ICAM-1, fibrinogen, C3bi and factor X.

Independent claim 1 recites "integrins" and "ligands" numerous times which renders the meaning and intention of the dependent claims ambiguous and confusing.

Applicant should amend the claims to clearly set forth the appropriate specificities.

Applicant is invited to provide claims that read on the elected invention only.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-6, 8, 10-12 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Genetta et al. (Ann Pharmacol. 30: 251-257, 1996), as evidenced by Schwarz et al. (Thrombosis Research 107: 121-128, 2002), Bendeck et al. (J Vasc Res 38: 590-599, 2001), Wu et al. (Thrombosis Research 101: 127-138, 2001) and The ERASER Investigators (Circulation 100: 799-806, 1999).

Genetta et al. teach the results of clinical trials which have indicated that abciximab can reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients, plays a role in the treatment of unstable angina and acute therapy of myocardial infarctions (see entire document, including Data Synthesis on page 251, column 1 and Clinical Trials on pages 253-254). It is noted that the patients were given bolus doses of 0.25 mg/kg antibodies prior to and after angioplasty (see pages 252-255).

Genetta et al. teach the mechanism of action of abciximab, including its ability to hinder platelets and fibrinogen from participating in platelet aggregation and to prevent von Willebrand factor binding (see page 252, column 2, Mechanism of Action).

However, Genetta et al. does not disclose the Mac-1-binding properties of abcixmab.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GP IIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abcixmab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, both Bendeck et al. and Wu et al. teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire document, including Abstract and Discussion).

The ERASER Investigators note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference note that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using abciximab in a number of thrombotic conditions, resulting in the inhibition or reduction of stenosis and/or restenosis. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In view of applicant's arguments of the record, the following is noted.

The claims recite inhibiting stenosis OR restenosis in an amount to inhibit or reduce stenosis OR dependent restenosis of a blood vessel following injury to vascular tissue.

The claims are not limited to inhibiting intimal hyperplasia associated with in-stent restenosis.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim terms are interpreted not only in light of the specification but also in light of the prior art. See In re Cortright, 49 USPQ2d 1464, 1467 (Fed. Cir. 1999).

Thus, the clinical use and ability of abciximab to reduce the incidence of abrupt closure and restenosis associated with PTCA performed in high risk patients and to play a role in the treatment of unstable angina and acute therapy of myocardial infarctions anticipates the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

15. Claims 1-6, 8 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995) (1449), as evidenced by Schwarz et al. (Thrombosis Research 107: 121-128, 2002), Bendeck et al. (J Vasc Res 38: 590-599, 2001), Wu et al. (Thrombosis Research 101: 127-138, 2001) and The ERASER Investigators (Circulation 100: 799-806, 1999).

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Simon et al. teach the Mac-1-dependent adhesion to fibrinogen and ICAM-1 which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines.

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GP IIb/IIIa-blocking antibody fragment abcixmab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abcixmab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, Bendeck et al. and Wu et al. teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire documents, including Abstracts and Discussions).

The ERASER Investigators note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference note that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In view of applicant's arguments of the record, the following is noted.

The claims recite inhibiting stenosis OR restenosis in an amount to inhibit or reduce stenosis OR dependent restenosis of a blood vessel following injury to vascular tissue.

The claims are not limited to inhibiting intimal hyperplasia associated with in-stent restenosis.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim terms are interpreted not only in light of the specification but also in light of the prior art. See In re Cortright, 49 USPQ2d 1464, 1467 (Fed. Cir. 1999).

Thus, the 7E3 antibody used to inhibit ischemic complications of coronary angioplasty and clinical restenosis anticipate the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

16. Claims 1-6, 8, 10-12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Coller et al. (U.S. Patent No. 5,976,532), as evidenced by Schwarz et al. (Thrombosis Research 107: 121-128, 2002), Bendeck et al. (J Vasc Res 38: 590-599, 2001), Wu et al. (Thrombosis Research 101: 127-138, 2001) and The ERASER Investigators (Circulation 100: 799-806, 1999).

Coller et al. teach the use of the 7E3 antibody to treat a number of thrombotic conditions, including providing 7E3 prior to angioplasty in effective amounts sufficient for inhibition of platelet aggregation as well as to prevent or reduce reocclusion that can occur after thrombolysis (see entire document, including Utility of Platelet-Specific Chimeric immunoglobulin in columns 5-7, Examples and Claims). Here, Coller et al. also teach that effective amounts can be given parenterally in pharmaceutical acceptable vehicles encompassed by the claimed limitations by administering the antibody before, alone with or subsequent to be administered with a thrombolytic agent or anticoagulant in amounts sufficient to prevent platelet aggregation that can result in reocclusion (Utility of Platelet-specific Chimeric Immunoglobulin). Antibody was given in dosages from 0.10- 0.30 mg / kg (e.g. see Example 3 on columns 11-15). It is noted that the severity of stenosis was reduced as visualized by angiography as well as by increase in the flow velocity signal (e.g. Case Report on columns 29-30, including column 29, lines 64-67). Coller et al. also teach that the antibodies can be used in a variety of situations including prevent thrombosis in a pulmonary embolism, transient ischemic attacks, deep vein thrombosis, coronary bypass surgery, surgery to insert a prosthetic vessel as well as angioplasty procedures encompassed by the claimed methods (see columns 5-6, overlapping paragraph).

Schwarz et al. describe the binding of abciximab to Mac-1, in particular the I-domain (also called A-domain) of the Mac-1α subunit (see entire document, including the Abstract, Results and Discussion).

Schwarz et al. provide evidence that the GP IIb/IIIa-blocking antibody fragment abciximab could inhibit the binding of fibrinogen, iC3b and the coagulation factor X to Mac-1 and that the adhesion of the THP-1 cells to immobilized ICAM-1 and to fibrinogen was reduced significantly by abcixmab (see entire document, including the Abstract).

In determining the mechanisms of action by which the beneficial treatment with c7E3 (abciximab, ReoPro) has been associated with a reduction in coronary events and the need for revascularization, Bendeck et al. and Wu et al. teach that the 7E3 antibody can reduce smooth muscle cell migration following vascular injury which resulted in a decrease in intimal size (see entire documents, including Abstracts and Discussions).

The ERASER Investigators note that potent platelet inhibition with abciximab does not reduce in-stent restenosis in their study (see entire document, including the Abstract). However, the reference note that these results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ (see page 805, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods using 7E3 antibodies in a number of thrombotic conditions, resulting in the inhibition or reduction of stenosis and/or restenosis.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

In view of applicant's arguments of the record, the following is noted.

The claims recite inhibiting stenosis OR restenosis in an amount to inhibit or reduce stenosis OR dependent restenosis of a blood vessel following injury to vascular tissue.

The claims are not limited to inhibiting intimal hyperplasia associated with in-stent restenosis.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim terms are interpreted not only in light of the specification but also in light of the prior art. See In re Cortright, 49 USPQ2d 1464, 1467 (Fed. Cir. 1999).

Thus, the 7E3 antibody used to inhibit ischemic complications of coronary angioplasty and clinical restenosis anticipate the claimed methods in the absence of a manipulative difference between the prior art methods and the broadest reasonable interpretation of the instant methods.

17. Claims 1-6, 8, 10-12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Co et al. (U.S. Patent No. 6,210,671) (see entire document).

Co et al. teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1). Co et al. teach that the antibodies can be administered before during or after the administration of thrombolytic agents or angioplasty, including doses of 0.01-10 mg/kg, 0.14-5 mg/kg and 0.3-3 mg/kg (column 18, paragraph 4). Co et al. teach administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would known or apparent to the skilled artisan (column 20, paragraph 1-4).

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients and methods steps even in major amounts. See MPEP 2111.03.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty resulting in the inhibition or reduction of stenosis and/or restenosis. Although the reference does not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be achieve by the administration of effective amounts (column 18, paragraph 4 and column 20, paragraphs 1-4 to column 21, paragraphs 1-2) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. columns 77-18, overlapping paragraph) targeted and encompassed by the claimed methods.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

18. Claims 1-6, 8, 10-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Todd et al. (U.S. Patent No. 4,935,234) (see entire document).

Todd et al. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- / Mac-1- specific antibodies (see entire document, including Claims). Todd et al. teach providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 2). Todd et al. exemplify 1 mg/kg dosing (e.g. see column 7, paragraph 1 and column 9, paragraph 1).

Todd et al. teach that myocardial ischemia results from occlusion, reperfusion in the presence of a critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4). One of ordinary skill in the art would have immediately envisaged that providing the anti-CD11b antibody in therapeutic methods would have encompassed providing the antibody in a pharmaceutical composition comprising at least a "solution" at the time the invention was made. One of ordinary skill in the art at the time the invention was made would have immediately envisaged that the referenced teaching the insertion of balloon catheters in the circulatory system would have referred to angioplasty at the time the invention was made.

The claim language is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims.
the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim.

Although the reference does not disclose the limitation of restenosis per se, these claimed endpoints would be achieve by the administration of effective amounts (e.g. to attenuate inflammatory responses (see column 1, paragraph 2; 1 mg/kg in column 7, paragraph 2 and reduce tissue damage, to inhibit undesired neutrophil functions in column 10, paragraph 1) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. column 10, paragraph 1) targeted and encompassed by the claimed methods

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods encompassed by the referenced combination therapy including the use of anti-CD11b antibodies in methods of therapeutic treatment of ischemia-reperfusion injuries resulting in the inhibition or reduction of stenosis and/or restenosis.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Also, see Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

19. Claims 1-6, 8, 10-12 are rejected under 35 U.S.C. § 103 as being unpatentable Co et al. (U.S. Patent No. 6,210,671) AND/OR Todd et al. (U.S. Patent No. 4,840,793) in view of Simon et al. (Circulation 92, 8 Suppl: I-110, Abstract 0519, 1995), Mazzone et al. (Circulation 88: 358-363, 1993, Ikeda et al. (Am Heart J. 128: 1091-1098, 1994), Inoue et al. JACC 28: 1127-1133 (1996), Rogers et al. (Circulation 88: 1215-1221, 1993).

Co et al. teach methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (see entire document, including columns 17-18, overlapping paragraph and column 18, paragraph 3-4) wherein the L-selectin-specific antibodies can used in combination with other humanized or human antibodies reactive with CD11b (i.e. Mac-1) (column 18, paragraph 1).

Co et al. teach that the antibodies can be administered before during or after the administration of thrombolytic agents or angioplasty, including doses of 0.01-10 mg/kg, 0.14-5 mg/kg and 0.3-3 mg/kg (column 18, paragraph 4).

Co et al. teach administering the antibodies parenterally in pharmaceutical compositions along with suitable carriers encompassed by the claimed invention in effective amounts that would known or apparent to the skilled artisan (column 20, paragraph 1-4).

Although the reference does not disclose the limitations of stenosis and restenosis per se, these claimed endpoints would be expected, intrinsic or desired endpoints by administering effective amounts (column 18, paragraph 4 and column 20, paragraphs 1-4 to column 21, paragraphs 1-2) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. columns 17-18, overlapping paragraph) targeted and encompassed by the claimed methods. The referenced methods of therapeutic and prophylactic treatment of ischemia-reperfusion injury in various modalities including cardiac surgery such as coronary artery bypass and elective angioplasty (columns 17-18, overlapping paragraph and column 18, paragraphs 3-4), the ordinary artisan would have had an expectation of success that anti-CD11b antibodies would have inhibited or reduced restenosis or stenosis.

Co et al. also differs from the not disclosing the use of anti-CD11b antibodies in the absence of L-selectin-specific antibodies per se.

Todd et al. teach methods of reducing tissue damage occurring at an inflammatory site in a host experiencing a phagocyte-mediated inflammatory conditions, including inflammation from myocardial infarction or ischemia-reperfusion injury and the insertion of balloon catheters in the circulatory system with CD11b- / Mac-1- specific antibodies (see entire document, including Claims).

Todd et al. teach providing the CD11b-specific antibodies prior to intervention as well as in single or multiple doses to attenuate the inflammatory responses (see column 1, paragraph 2).

Todd et al. exemplify 1 mg/kg dosing (e.g. see olumn 7, paragraph 1 and column 9, paragraph 1).

Todd et al. teach that myocardial ischemic results from occlusion, reperfusion in the presence of a critical stenosis or narrowing of a blood vessel (e.g. column 6, paragraph 4).

One of ordinary skill in the art at the time the invention was made would have readily understood that the referenced teaching the insertion of balloon catheters in the circulatory system would have referred to angioplasty.

Although the reference does not disclose the limitation of restenosis per se, these claimed endpoints would have been expected or desired endpoints by administering effective amounts (e.g. to attenuate inflammatory responses (see column 1, paragraph 2; 1 mg/kg in column 7, paragraph 2 and reduce tissue damage, to inhibit undesired neutrophil functions in column 10, paragraph 1) of CD11b / Mac-1-specific antibodies in the same patient populations (e.g. column 10, paragraph 1) targeted and encompassed by the claimed methods.

Simon et al. teach that the 7E3 antibody is used to inhibit ischemic complications of coronary angioplasty and clinical restenosis and that this 7E3 antibody cross-reacts with Mac-1 (see Abstract).

Simon et al. teach the Mac-1-dependent adhesion to fibrinogen and ICAM-1, ligands which are abundant in vessels walls and that Mac-1-expressing cells accumulate in restenosis lesions and have the potential to interact with other vascular cells by secreting growth factors and cytokines.

Simon et al. teach that the cross-reactivity of c7E3 with Mac-1 may play an additional role in inducing passivity of the vessel wall.

Therefore, Simon et al. provides additional motivation to target Mac-1 in therapeutic interventions associated with the complications of angioplasty including restenosis.

The following references provides further support for targeting Mac-1 in the treatment of complications of angioplasty including restenosis.

Mazzone et al. teach the CD11b/CD18 plays a major role in the leukocyte adhesion process and can be upregulated severalfold in response to chemotactic factors (see Background). Mazzone et al. further teach that patients with unstable angina have an increased expression of granulocyte and monocyte CD11b/CD18, indicating that an inflammatory reaction takes place with their coronary tree. Activation of these leukocytes may induce coronary vasoconstriction, favor thrombotic processes, and further activate platelets, thus having potential implications on the pathogenesis of unstable coronary artery disease (see Conclusion). The Discussion provides a teaching of the importance of CD11/CD18 in tissue injury in vivo in a number of animal models, including that the addition of anti-CD18 antibodies can reduce tissue injury and mortality in ischemia reperfusion injury-induced shock and myocardial infarct size (see Discussion on page 360, column 1).

Ikeda et al. teach the surface expression of CD11b of neutrophils increased significantly after percutaneous transluminal coronary angioplasty (PTCA) (see entire document, including Abstract, Results and Discussion). Ikeda et al. teach anti-CD11b antibody inhibits several neutrophil functions, including the binding of C3bi-opsonized particles, adhesive interactions of neutrophils, spreading on vascular endothelium and chemotaxis (see Discussion, particularly page 1095, column 2). Ikeda et al. further teach that anti-CD11b antibodies significantly reduced neutrophil accumulation within the infarct area (see Discussion, particularly page 1095, column 2). With respect to restenosis, Ikeda et al. teach that neutrophil activation after PTCA in humans appears to play an important role in the initial step of inflammatory phase and then to trigger the pathophysiologic chain reaction eventually resulting in coronary restenosis (see Clinical Implications on page 1096-1097). Ikeda et al. note here that activated neutrophils can potentiate platelet activity, in turn, leading to vasoconstriction and proliferation of vascular smooth muscle.

Inoue et al. teach inflammatory stimuli within the coronary vessels associated with coronary angioplasty upregulate Mac-1 expression on the surface of PMNs and this process is more marked in patients who experience later restenosis (see entire document, including Conclusions). The activation of neutrophil adhesion molecule after PTCA has valued as a predictor of subsequent restenosis (see Conclusion). Inoue et al. teach that the same cytokines that stimulate the expression of leukocyte adhesion molecules, such as Mac-1 also stimulate smooth muscle cell proliferation.

Rogers et al. teach that the inhibition of neointimal hyperplasia and thrombosis depends on the type of vascular injury and the site of drug administration (see entire document, including Abstract and Discussion). Here, Rogers et al. teach "Different forms of injury may require different therapeutics and complication of arterial intervention such as excessive neointimal hyperplasia and thrombosis may demand alternative therapeutic regimens. Duration, dose, and site of delivery rather that frank resistance to therapy may explain why experimental effective antiproliferative and antithrombotic agents fail clinically."

Although certain references do not disclose the targeted endpoint of reducing or inhibiting stenosis or restenosis per se, it was clear that the references do teach targeting Mac-1 with effective amounts encompassed by the claimed invention (e.g. 0.25 mg/kg or more in single or multiple doses) in order to inhibit various inflammatory consequences of Mac-1 expressing cells in therapeutic regimens associated with stenosis or restenosis such as angioplasty or bypass surgery. In addition, the combined references do teach targeting either stenosis, restenosis or endpoints associated with stenosis or restenosis (occlusion, intimal hyperplasia). The claimed methods comprises the same steps, the same effective amounts and the same targeted patient populations as the prior art. In addition, Rogers et al. teach duration, dose, and site of delivery are important in achieving therapeutic endpoints aimed at limiting restenosis such as inhibiting intimal hyperplasia (see entire document). Given the well known complications of stenosis and restenosis associated with various procedures such as angioplasty or bypass surgery at the time the invention was made, one of ordinary skill in the art would have had an expectation of success that treating these conditions or procedures with effective amounts of anti-Mac-1 antibodies would have resulted in the inhibition or reduction of certain endpoints associated with stenosis or restenosis.

The different references differ from the claimed methods by not disclosing all of the known targeted conditions complicated by stenosis or restenosis as recited in claim 3.

Given the combined teachings which including teachings of administering antibodies that bind Mac-1 / CD11b to treat or to prophylactically treat a number of thrombotic conditions such as angioplasty and bypass surgery encompassed by the claimed methods, one of ordinary skill in the art would have been motivated to apply anti-Mac-1 antibodies to inhibit or reduce stenosis or restenosis in these various modalities with an expectation of success at the time the invention was made. It was well known by the ordinary artisan at the time the invention was made that angioplasty, atherectomy endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery or transplantation of cells, tissues or organs was complicated by stenosis or restenosis.

Given the various targeted applications such as cardiac surgery (coronary artery bypass) and angioplasty as well as transplantation as taught by Co et al. (e.g. columns 17-18) and Todd et al. (e.g. Summary of the Invention and Detailed Description) as well as the conditions including restenosis as indicated in the secondary references, one of ordinary skill in the art would have targeted Mac-1 to inhibit the contribution of inflammatory cells such as neutrophils to the occlusion of blood vessels such as stenosis or restenosis in various conditions at the time the invention was made. Therefore, it would have been obvious to target those conditions recited in claim 3 at the time the invention was made.

Further, the composition forms set forth in claim 4 were well known and practiced at the time the invention was made. Also see columns 20-21 of Co et al. Note that Rogers et al. teach that duration, dose, and site of delivery were important in achieving therapeutic endpoints aimed at limiting restenosis such as inhibiting intimal hyperplasia.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-6, (7), 8 (9) and 10-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of copending application USSN 09/776,533. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same or nearly the same methods of inhibiting stenosis or restenosis in the same or nearly the same methods of cardiovascular condition with the same anti-Mac-1 antibodies, as the elected invention.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

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